

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference SJKBP6234025	FOR FURTHER ACTION	See item 4 below
International application No. PCT/GB2004/002739	International filing date (<i>day/month/year</i>) 25 June 2004 (25.06.2004)	Priority date (<i>day/month/year</i>) 25 June 2003 (25.06.2003)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant PROTEOME SCIENCES PLC		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).
2. This REPORT consists of a total of 12 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the report |
| <input checked="" type="checkbox"/> | Box No. II | Priority |
| <input checked="" type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/> | Box No. VI | Certain documents cited |
| <input checked="" type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input type="checkbox"/> | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35	Date of issuance of this report 03 January 2006 (03.01.2006) Authorized officer <div style="text-align: center; font-weight: bold;">Dorothee Mülhausen</div> Telephone No. +41 22 338 87 40
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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

REC'D 12 JAN 2005

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To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/GB2004/002739

International filing date (day/month/year)
25.06.2004

Priority date (day/month/year)
25.06.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/48, G01N33/68, C12Q1/42

Applicant
PROTEOME SCIENCES PLC

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/002739

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☒ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/002739

Box No. II Priority

1. ☐ The following document has not been furnished:

☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ It has not been possible to consider the validity of the priority claim because a copy of the priority document was not available to the ISA at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/002739

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 46-48 (in part)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 46-48 (in part)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/GB2004/002739

**Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or
Industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	49,50
	No: Claims	1-48,51,52
Inventive step (IS)	Yes: Claims	
	No: Claims	1-52
Industrial applicability (IA)	Yes: Claims	1-52
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

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Re Item III.

Present claims 46-48 relate to compounds defined by reference to a desirable characteristic or property, namely compounds that are identified by the method of claims 1-43. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for no such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for the screening method per se.

Re Item V.

- 1 The following documents are referred to in this communication:
 - D1 MEIJER L ET AL: "INHIBITION OF CYCLIN-DEPENDENT KINASES, GSK-3SS AND CK1 BY HYMENIALDISINE, A MARINE SPONGE CONSTITUENT" CHEMISTRY AND BIOLOGY, CURRENT BIOLOGY, LONDON, GB, vol. 7, no. 1, January 2000 (2000-01), pages 51-63, XP000901413 ISSN: 1074-5521
 - D2 US 6 057 117 A (RING DAVID B ET AL) 2 May 2000 (2000-05-02)
 - D3 LEE G ET AL: "Tyrosine phosphorylation of tau" SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 27, no. 1, 2001, page 1436, XP002308830 &; 31ST ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE; SAN DIEGO, CALIFORNIA, USA; NOVEMBER 10-15, 2001 ISSN: 0190-5295
 - D4 WO 95/19178 A (RES FOUND MENTAL HYGIENE) 20 July 1995 (1995-07-20)

2 NOVELTY (Article 33(2) PCT)

2.1 CLAIM 1

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is not new in the sense of Article 33(2) PCT.

Document D1 discloses (the references in parentheses applying to this

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document): Use of casein kinase 1, or a nucleic acid molecule encoding the casein kinase 1 (p. 51, abstract), for screening for candidate compounds which are capable of (a) inhibiting the activity of casein kinase 1 in phosphorylating a tau protein or (b) binding to casein kinase 1 to inhibit its interaction with a tau protein (p. 51, abstract; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29).

2.2 CLAIM 22

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 22 is not new in the sense of Article 33(2) PCT.

Document D1 discloses (the references in parentheses applying to this document): A method of screening for substances which are capable of inhibiting the phosphorylation of a tau protein by casein kinase 1 (CK1) (p. 51, abstract), wherein the tau protein comprises one or more phosphorylation sites (p. 51, abstract; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29), the method comprising:

- a) contacting at least one candidate substance, the tau protein and casein kinase 1 under conditions in which the casein kinase 1 is capable of phosphorylating the site(s) of the tau protein in the absence of the candidate substance (p. 51, abstract; p. 52, col. 2, l. 2 to p. 53, col. 1, l. 26; table 1; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29);
- b) determining whether, and optionally the extent to which, the candidate substance inhibits the phosphorylation of the tau protein at one or more sites of the tau protein by casein kinase 1 (p. 51, abstract; p. 52, col. 2, l. 2 to p. 53, col. 1, l. 26; table 1; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29); and,
- c) selecting the candidate substance which inhibits phosphorylation of the tau protein at one or more of the sites (p. 51, abstract; p. 52, col. 2, l. 2 to p. 53, col. 1, l. 26; table 1; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29).

2.3 CLAIMS 44 and 45

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 44 and 45 is not new in the sense of Article 33(2) PCT.

Document D1 discloses (the references in parentheses applying to this document): A method of preparing a pharmaceutical composition or medicament (p. 51, abstract; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29), the method comprising:

- (i) identifying a casein kinase 3 inhibitor according to any one of claims 1 to 43 (p. 51, abstract; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29);
- (ii) optimising the structure of the casein kinase 1 inhibitor (p. 51, abstract; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29); and

(iii) preparing the pharmaceutical composition or medicament containing the optimised casein kinase 1 inhibitor (p. 51, abstract; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29).

2.4 CLAIMS 46 AND 47

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 46 and 47 is not new in the sense of Article 33(2) PCT. Document D1 discloses (the references in parentheses applying to this document): A substance obtainable by the method of any one of claims 1 to 43 and its use for the preparation of a medicament for the treatment of a tauopathy (p. 51, abstract; p. 61, col. 1, l. 10-29).

2.5 CLAIM 51

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 51 is not new in the sense of Article 33(2) PCT.

Document D1 discloses (the references in parentheses applying to this document): A method of screening for substances which are capable of inhibiting phosphorylation by a kinase at one or more of the site(s) of a tau protein selected from the group consisting of S68, T69, T71, (T111/S113), S191, S258, S289 (T414/S416), T427, S433, S435 and Y394 (p. 51, abstract; p. 52, col. 2, l. 2 to p. 53, col. 1, l. 26; table 1; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29), the method comprising:

- a) contacting at least one candidate substance, a tau protein which comprises one or more of the phosphorylation sites and a kinase which is capable of phosphorylating the tau protein under conditions in which the kinase is capable of phosphorylating one or more of the sites of the tau protein in the absence of the candidate substance (p. 51, abstract; p. 52, col. 2, l. 2 to p. 53, col. 1, l. 26; table 1; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29);
- b) determining whether, and optionally the extent to which, the candidate substance inhibits the phosphorylation of the tau protein at one or more sites of the tau protein (p. 51, abstract; p. 52, col. 2, l. 2 to p. 53, col. 1, l. 26; table 1; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29); and,
- c) selecting the candidate substance which inhibits phosphorylation of the tau protein at one or more of the sites (p. 51, abstract; p. 52, col. 2, l. 2 to p. 53, col. 1, l. 26; table 1; p. 59, col. 1, l. 49 to p. 60, col. 1, l. 9; p. 60, col. 2, l. 51 to p. 61, col. 1, l. 29).

2.6 CLAIM 52

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 52 is not new in the sense of Article 33(2) PCT.

Document D4 discloses (the references in parentheses applying to this document): A method of screening for substances which are capable of promoting dephosphorylation of a tau protein by a phosphatase at one or more of the site(s) of a tau protein selected from the group consisting S68, T69, T71, (T111/S113), S191, S258, S289 (T414/S416), T427, S433, S435 and Y394 the method comprising (p. 1, l. 8-13; p. 5, table 1; p. 9, l. 9-23; p. 17, l. 14 to p. 18, l. 4):
a) contacting at least one candidate substance, a tau protein comprising one or more the phosphorylation site and a phosphatase which is capable of dephosphorylating the tau protein under conditions in which the phosphatase is capable of dephosphorylating the site(s) of the tau protein in the absence of the candidate substance (p. 1, l. 8-13; p. 5, table 1; p. 9, l. 9-23; p. 17, l. 14 to p. 18, l. 4);

b) determining whether, and optionally the extent to which, the candidate substance promotes the dephosphorylation of the tau protein at one or more sites of the tau protein (p. 1, l. 8-13; p. 5, table 1; p. 9, l. 9-23; p. 17, l. 14 to p. 18, l. 4); and,

c) selecting the candidate substance which promotes dephosphorylation of the tau protein at one-or more of the sites (p. 1, l. 8-13; p. 5, table 1; p. 9, l. 9-23; p. 17, l. 14 to p. 18, l. 4).

2.7 Dependent claims 2-21 and 23-43, 45 and 48 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

3 INVENTIVE STEP (Article 33(3)PCT)

3.1 CLAIMS 49 AND 50

The present application does not meet the criteria of Article 33(1) PCT, because the subject matter of claims 49 and 50 does not involve an inventive step in the sense of Article 33(3)PCT.

3.1.1 Document D2, which is considered to represent the most relevant state of the art to the subject matter of claim 49, discloses (the references in parentheses

applying to this document): A method of screening for substances which are capable of inhibiting the phosphorylation of a tau protein by glycogen synthase kinase 3 (GSK3).

- 3.1.2 The subject-matter of independent claims 49 and 50 differs from the disclosure of D2 in that method identifies substances which are capable of inhibiting the phosphorylation of a tau protein by fyn. No technical effect seems derivable from this difference.
- 3.1.3 The problem to be solved by the present invention may therefore be regarded as: How to provide a further method for identifying substances which are capable of inhibiting the phosphorylation of a tau.
- 3.1.4 In view of D2 the solution proposed in claims 49 and 50 of the present application cannot be considered as involving an inventive step (Article 33(3) PCT) for the following reasons: D3 discloses that tau is phosphorylated at a terminal tyrosine residue by fyn. Starting from the closest prior art a skilled person intending to solve the objective technical problem under 3.1.3 would also consider the teaching of D3 to arrive at the solution which claims 49 and 50 provide.

4 INDUSTRIAL APPLICABILITY

The present application fulfils the requirements of Article 33(1) PCT because the subject-matter of claims 1-52 is industrially applicable in the sense Article 33(4) PCT.

Re Item VII.

- 5 Although claims 44 and 45 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.
- 6 Although claims 1, 22 and 49-51 have been drafted as separate independent

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claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought and/or in respect of the terminology used for the features of that subject-matter. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

- 7 It appears that a problem in the numbering of the claims has occurred. After claim 49, the remaining claims are numbered 48-50. For the analysis of the present application, the claims have been renumbered 50-52.

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